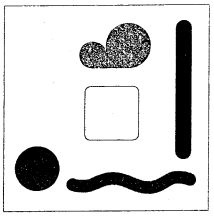

RCC PROJECT 688983

WACKER BS 1701:

ACUTE ORAL TOXICITY STUDY IN RATS

REPORT

Author: G. Arcelin

Sponsor: Wacker-Chemie GmbH
Werk Burghausen
Johannes-Hess-Str. 24
D-84489 Burghausen
Germany

Study Completion: 29-JUN-1998

RCC

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1. PREFACE

1.1 GENERAL

Title	WACKER BS 1701: Acute Oral Toxicity Study in Rats
Sponsor	Wacker-Chemie GmbH Werk Burghausen Johannes-Hess-Str. 24 D-84489 Burghausen Germany
Monitoring Scientist	Dr. Axel Bosch
Testing Facility	RCC, Research & Consulting Company Ltd. c/o BRL, Biological Research Laboratories Ltd. Wölferstrasse 4, CH-4414 Füllinsdorf / Switzerland
RCC Project Number	688983
Test Article	WACKER BS 1701
Test System	Rat

1.2 PROJECT STAFF

Study Director	G. Arcelin
Technical Coordinator	R. König

1.3 SCHEDULE

Acclimatization	07-APR-1998 to 13-APR-1998 (males) 21-APR-1998 to 27-APR-1998 (females)
Treatment	14-APR-1998 (males) 28-APR-1998 (females)
Observation	14-APR.-1998 to 28-APR-1998 (males) 28-APR-1998 to 12-MAY-1998 (females)
Termination	28-APR-1998 (males) 12-MAY-1998 (females)
Report	29-JUN-1998

1.4 ARCHIVING

Research & Consulting Company Ltd., CH-4452 Itingen will archive the following data for at least 10 years:

protocol, report, raw data and test article reference sample. No data will be discarded without the Sponsor's consent.

1.5 PROJECT STAFF SIGNATURES

Study Director: G. Arcelin

Date: 29-JUN-1998

Management: T.R. Allen

Date: 29-JUN-1998

1.6 QUALITY ASSURANCE STATEMENT

RCC, Research & Consulting Company Ltd., CH-4452 Itingen / Switzerland

PROJECT NUMBER	:	688983
TEST ARTICLE	:	WACKER BS 1701
STUDY DIRECTOR	:	G. Arcelin
TITLE	:	WACKER BS 1701: Acute Oral Toxicity Study in Rats

Study procedures were periodically inspected and this report was audited by the RCC Quality Assurance Unit. The dates are given below.

Dates of QAU Inspections / Audits	Dates of Reports to the Study Director and to Management
07-APR-1998	07-APR-1998
15-APR-1998	15-APR-1998
29-APR-1998	29-APR-1998
24-JUN-1998	25-JUN-1998

Manager, Quality Assurance Unit: Dr. G. Menne

Date: 29 - Jun - 1998

GOOD LABORATORY PRACTICE

1.7 STATEMENT OF COMPLIANCE / GLP GUIDELINES

PROJECT NUMBER	:	688983
TEST ARTICLE	:	WACKER BS 1701
STUDY DIRECTOR	:	G. Arcelin
TITLE	:	WACKER BS 1701: Acute Oral Toxicity Study in Rats

This study was conducted in compliance with the following Good Laboratory Practice Regulations:

Good Laboratory Practice (GLP) in Switzerland, Procedures and Principles, March 1986.

OECD Principles of Good Laboratory Practice, Environment Monograph Number 45. OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring - Number 1. Environment Directorate, Organization for Economic Co-operation and Development, Paris 1992.

There were no circumstances that may have affected the quality or integrity of the data.

Study Director: G. Arcelin

G. Arcelin

Date: 29-JUN-1998

1.8 TEST GUIDELINES

The study procedures described in this report are based on the following guidelines:

OECD Guidelines for Testing of Chemicals, Number 423 "Acute Oral Toxicity", adopted March 22, 1996.

Directive 96/54/EEC, B.1 tris "Acute Toxicity-Oral-Acute Toxic Class Method", September 30, 1996.

1.9 ACCREDITATION

The testing laboratory "RCC, Research & Consulting Company Ltd." is accredited according to EN 45001 under accreditation number STS 085 by the Swiss Accreditation Service.

2. SUMMARY OF RESULTS

Two groups, each using three male or three female HanIbm: WIST (SPF) rats, were treated with WACKER BS 1701 at 2000 mg/kg by oral gavage. The test article was diluted in vehicle (corn oil) at a concentration of 0.2 g/ml and administered at a volume of 10 ml/kg. The animals were examined for clinical signs four times during test day 1 and once daily during test days 2-15. Mortality/viability were recorded together with clinical signs at the same time intervals. Body weights were recorded on day 1 prior to administration and on days 8 and 15. All animals were necropsied and examined macroscopically.

No deaths occurred during the study.

No clinical signs of toxicity were observed during the observation period.

The body weight of the animals was within the range commonly recorded for animals of this strain and age.

No macroscopic findings were observed at necropsy.

3. CONCLUSION

The median lethal dose of WACKER BS 1701 after single oral administration to rats of both sexes, observed over a period of 14 days, could not be estimated as no death occurred.

LD_{50} : greater than 2000 mg/kg

4. OBJECTIVE

4.1 PURPOSE AND RATIONALE

The purpose of this study was to assess the acute oral toxicity of WACKER BS 1701 when administered by single oral gavage to rats, followed by an observation period of 14 days.

This study should provide a rational basis for risk assessment.

5. MATERIALS AND METHODS
Experimental Design

5.1 TEST SYSTEM

Test system	Rat, HanIbm: WIST (SPF)
Rationale	Recognized by the international guidelines as a recommended test system.
Source	BRL, Biological Research Laboratories Ltd. Wölferstrasse 4, CH-4414 Füllinsdorf / Switzerland
Number of animals per group	3 males or 3 females
Total number of animals	3 males 3 females
Age when treated	Males: 8 weeks Females: 10 weeks
Body weight range when treated	Males: 206 – 216 g Females: 171 - 190 g
Identification	By unique cage number and corresponding color-coded spots on the tail.
Acclimatization	One week under laboratory conditions, after health examination. Only animals without any visible signs of illness were used for the study.

5.2 HUSBANDRY

Room no.	101 / BRL
Conditions	**Standard Laboratory Conditions** Air-conditioned with 10-15 air changes per hour and continuously monitored environment with a target range for room temperature of 22 ± 3 °C, and for relative humidity between 40-66 %. The animals were provided with a 12-hour light, 12-hour dark cycle. Music was played during the light period.
Accommodation	Groups of three in Makrolon type-4 cages with standard softwood bedding ("Lignocel", Schill AG, CH-4132 Muttenz)
Diet	Pelleted standard Kliba 3433, batch nos. 94/97 and 20/98 rat maintenance diet (Kliba Mühlen AG, CH-4303 Kaiseraugst) available *ad libitum* (except for the overnight fasting period prior to intubation). Results of analyses for contaminants are archived at RCC.
Water	Community tap water from Füllinsdorf, available *ad libitum*. Results of bacteriological, chemical and contaminant analyses are archived at RCC.

5.3 TEST ARTICLE (ACCORDING TO INFORMATION PROVIDED BY THE SPONSOR)

Identification	WACKER BS 1701
Description	liquid
Batch number	1244KH
Purity / Formulation	≥ 95 % (2,4,4-Trimethylpentyltriethoxysilane and isomers)
Stability of test article	Stable under storage conditions; expiration date: March, 2000
Stability of test article dilution	Stable in corn oil, for at least 4 hours.
Storage conditions	In the original container at room temperature away from direct sunlight.
Safety precautions	Routine hygienic procedures were used to ensure the health and safety of the personnel.

5.4 TEST ARTICLE PREPARATION

The test article was placed into a glass beaker on a tared Mettler PM 460 balance and the vehicle (corn oil) was added. A weight by volume dilution was prepared using a magnetic stirrer as homogenizer. Homogeneity of the test article in the vehicle was maintained during treatment.

The preparation was made shortly before dosing.

During formulation trials performed before treatment start the test article was readily soluble in corn oil.

5.5 TREATMENT

The animals received a single dose of the test article on a mg/kg body weight basis by oral gavage following fasting for approximately 17.5 to 19.5 hours, but with free access to water. Food was provided again approximately 3.5 hours after dosing.

Dose / kg body weight	2000 mg
Application volume / kg body weight	10 ml
Rationale	Oral administration was used as this is one possible route of human exposure during manufacture, handling and use of the test article.

5.6 OBSERVATIONS

Mortality / Viability	Four times during test day 1 and once daily during days 2-15.
Body weights	On test day 1 (pre-administration), 8 and 15.
Clinical signs	Each animal was examined for changes in appearance and behaviour four times during day 1, and once daily during days 2-15. All abnormalities were recorded.

5.7 PATHOLOGY

NECROPSY

Necropsies were performed by experienced prosectors. At the end of the observation period all animals were sacrificed by intraperitoneal injection of NARCOREN (Rhône Merieux GmbH, D-88471 Laupheim) at a dose of at least 2.0 ml/kg body weight (equivalent to at least 320 mg sodium pentobarbitone/kg body weight). The animals were examined macroscopically and all abnormalities recorded. Thereafter, they were discarded.

5.8 STATISTICAL ANALYSIS

No statistical analysis was used as no deaths occurred.

5.9 DATA COMPILATION

Body weights were recorded on-line.

Mortality/viability*, clinical signs and macroscopic findings were compiled into the RCC computer system during recording.

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* The computerised system does not show that the mortality/viability checks were recorded at the same time as the clinical signs.

6. RESULTS

6.1 MORTALITY

No deaths occurred during the study.

6.2 CLINICAL SIGNS

No clinical signs of toxicity were observed during the study period.

See pp. 17-18

6.3 BODY WEIGHTS

The body weight of the animals was within the range commonly recorded for animals of this strain and age.

See p. 20

6.4 MACROSCOPIC FINDINGS

No macroscopic findings were observed at necropsy.

See pp. 22-23

6.5 MEDIAN LETHAL DOSE

The median lethal dose of WACKER BS 1701 after single oral administration to rats of both sexes, observed over a period of 14 days, could not be estimated as no death occurred.

LD_{50} : greater than 2000 mg/kg

APPENDIX A

CLINICAL SIGNS

RCC PROJECT 688983
WACKER BS 1701

CLINICAL SIGNS
MALES
GROUP 1 (2000 MG/KG)

Test day	1	1	1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Time after treatment. Hours:	1	2	3	5														

ANIMAL NUMBER	SIGNS	MAX. GRADE
1	NO CLINICAL SIGNS NOTED	
2	NO CLINICAL SIGNS NOTED	
3	NO CLINICAL SIGNS NOTED	

- = sign not observed / . = observation not performed / + = animal dead

RCC PROJECT 688983
WACKER BS 1701

CLINICAL SIGNS
FEMALES
GROUP 2 (2000 MG/KG)

Test day Time after treatment. Hours:	1 1	1 2	1 3	1 5	2	3	4	5	6	7	8	9	10	11	12	13	14	15

ANIMAL NUMBER	SIGNS	MAX. GRADE
4	NO CLINICAL SIGNS NOTED	
5	NO CLINICAL SIGNS NOTED	
6	NO CLINICAL SIGNS NOTED	

- = sign not observed / . = observation not performed / + = animal dead

APPENDIX B

BODY WEIGHTS

RCC PROJECT 688983
WACKER BS 1701

BODY WEIGHTS (GRAM)

GROUP / SEX	ANIMAL	DAY 1	DAY 8	DAY 15
GROUP 1 / MALES (2000 MG/KG)	1	215.6	264.8	300.6
	2	205.9	243.3	275.0
	3	206.7	245.8	266.3
	MEAN	209.4	251.3	280.6
	ST.DEV.	5.4	11.7	17.8
	N	3	3	3
GROUP 2 / FEMALES (2000 MG/KG)	4	190.4	212.0	224.3
	5	181.8	194.7	210.5
	6	170.8	187.6	204.9
	MEAN	181.0	198.1	213.2
	ST.DEV.	9.8	12.6	10.0
	N	3	3	3

APPENDIX C

MACROSCOPIC FINDINGS

RCC PROJECT 688983
WACKER BS 1701

MACROSCOPIC FINDINGS
MALES
GROUP 1 (2000 MG/KG)

ANIMAL 1 (SCHEDULED NECROPSY, 28-APR-98, DAY 15 AFTER TREATMENT)

NO FINDINGS NOTED

ANIMAL 2 (SCHEDULED NECROPSY, 28-APR-98, DAY 15 AFTER TREATMENT)

NO FINDINGS NOTED

ANIMAL 3 (SCHEDULED NECROPSY, 28-APR-98, DAY 15 AFTER TREATMENT)

NO FINDINGS NOTED

RCC PROJECT 688983
WACKER BS 1701

MACROSCOPIC FINDINGS
FEMALES
GROUP 2 (2000 MG/KG)

ANIMAL 4 (SCHEDULED NECROPSY, 12-MAY-98, DAY 15 AFTER TREATMENT)

NO FINDINGS NOTED

ANIMAL 5 (SCHEDULED NECROPSY, 12-MAY-98, DAY 15 AFTER TREATMENT)

NO FINDINGS NOTED

ANIMAL 6 (SCHEDULED NECROPSY, 12-MAY-98, DAY 15 AFTER TREATMENT)

NO FINDINGS NOTED

APPENDIX D

CERTIFICATION

- **ACCREDITATION / EUROPEAN STANDARD EN 45001**

- **GLP – CERTIFICATION**

RCC PROJECT 688983
WACKER BS 1701

S SCHWEIZERISCHER PRÜFSTELLENDIENST
T SERVICE SUISSE D'ESSAI
S SERVICIO DI PROVA IN SVIZZERA
SWISS TESTING SERVICE

ACCREDITATION

EUROPEAN STANDARD EN 45001

RCC Research & Consulting Company Ltd.
Zelgliweg 1
CH-4452 Itingen/BL

This study is performed by the Testing Laboratory for
the toxicological investigation of
Pharmaceuticals and Medical Devices, Agrochemicals,
Industrial Chemicals, Food- and Feed-Additives
in accordance with

SN EN 45001

under accreditation number

STS 085

The accredited scope of testing is defined in the "STS Directory of the Swiss Accreditation Service".

To comply with this European Standard RCC is obliged to make the following statements:

- The test results relate only to the items tested.
- Information on the error of measurement (confidence interval, where relevant) can be requested.
- This report shall not be reproduced, except in full, without the written approval of the testing laboratory.

RCC PROJECT 688983
WACKER BS 1701

EIDGENÖSSISCHES DEPARTEMENT DES INNERN
DÉPARTEMENT FÉDÉRAL DE L'INTÉRIEUR
DIPARTIMENTO FEDERALE DELL'INTERNO

GLP Compliance Statement

It is hereby certified that

on February 12-16, 1996
February 19-23, 1996
June 14, 1996

the testing facilities of RCC Holding Company Ltd
4414 Füllinsdorf
Switzerland

were inspected by the Federal Office of Public Health, the Federal Office of Environment, Forests and Landscape and the Intercantonal Office for the Control of Medicaments with respect to the compliance with the Swiss GLP Principles. The inspection was performed in agreement with the OECD Guidelines for National GLP Inspections and Audits and comprised the following testing facilities:

- RCC Research and Consulting Company Ltd, Itingen
- RCC Umweltchemie AG, Itingen
- RCC Pharmanalytics Ltd, Itingen
- BRL Biological Research Laboratories Ltd/Microbiology, Füllinsdorf

It was found that the aforementioned testing facilities were operating in compliance with the Swiss Principles of Good Laboratory Practice (Good Laboratory Practice [GLP] in Switzerland, Procedures and Principles, March 1986) at the time they were inspected.

FEDERAL DEPARTMENT OF THE INTERIOR

Bern, July 9, 1996

Ruth Dreifuss
Federal Councillor